

Therapeutic management of canine atopic dermatitis by combination of pentoxifylline and PUFAs

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Canine atopic dermatitis (CAD) is a chronic, pruritic, and relapsing inflammatory skin disease that occurs in 10–15% of the canine population. CAD thereby constitutes a serious medical problem in veterinary medicine and is reported to be one of the most common causes of canine pruritus (Saridomichelakis *et al.*, 1999). The development and severity of the disease are related to a complex interaction between genetic, immunological, environmental, pharmacological, and physiological factors, as well as to the functional state of skin barriers. Increased phosphodiesterase (PDE) activity has been reported in dogs (Chan *et al.*, 1985) and humans with AD (Hanifin *et al.*, 1996), which seems to be responsible for the deficiency of cAMP response in atopic people (Butler *et al.*, 1983) and dogs (Butler *et al.*, 1983; Emala *et al.*, 1995). Dogs with CAD may have a disorder of fatty acid metabolism. A reduction in *n*6 fatty acid products of the Δ 6- and Δ 5- desaturases in erythrocytes of dogs with CAD in comparison with healthy housemates had been demonstrated by Fuhrmann *et al.* (2006).

Symptomatic treatment modalities for CAD include glucocorticoids, antihistamines, cyclosporine or a combination is usually tried, and fatty acid supplementation (Griffin, 1993; Scott *et al.*, 2001). Recently, several clinical studies have proven the use of cyclosporine (Olivry *et al.*, 2002; Steffan *et al.*, 2004; Thelen *et al.*, 2006; Kovalik *et al.*, 2007; Lucas *et al.*, 2007), azathioprine (Favrot *et al.*, 2007), fexofenadine (Plevnik *et al.*, 2006) and tacrolimus (Bensignor & Olivry, 2005; Marsella, 2005) with varying efficacy for treatment of CAD but none has displayed substantial activity. The adverse events of cyclosporine therapy in dogs are mainly intermittent vomiting, diarrhea (Thelen *et al.*, 2006), and hypertension (Lucas *et al.*, 2007). The only specific treatment for CAD is avoidance of major allergens and allergen-specific immunotherapy. Lack of serum IgE autoantibodies specific for AD in dogs with moderate and severe disease has been demonstrated by Olivry *et al.* (2008). Physicians should constantly attempt to decrease unnecessary glucocorticoid exposure via introduction of glucocorticoid-sparing therapies and tapering of glucocortic-

oids to a minimal effective dose (McDonough *et al.*, 2008). Spontaneous remission of clinical sign is rare, and avoidance of major allergens is often impossible (Scott *et al.*, 2001). Allergen-specific immunotherapy must usually be pursued for months before an improvement in clinical signs is observed, and it is not effective in all patients (Mueller, 1993; Scott *et al.*, 1993). Many of these dogs experience side-effects related to treatment, or do not achieve sufficient control of the disease. For these reasons, symptomatic therapies are often explored and calls for a look into new treatment strategies.

Pentoxifylline (PTX) is a member of the class of drugs that inhibit nonselectively phosphodiesterase (PDE) enzymes, referred to as PDE inhibitors (Marks *et al.*, 2001; Scott *et al.*, 2001). It also decreases fibronectin, reduces the production of cytokines (tumor necrosis factor- α , interleukin-1, interleukin -6, and interleukin-8), decreases leukocyte response to interleukins, impairs T-lymphocyte binding to keratinocytes, decreases fibroblastic activity and with long-term use, may decrease fibrosis (Samlaska & Winfield, 1994; Bruyzeel *et al.*, 1995). PTX has been reported to have a steroid-sparing effect in dogs and humans (Marsella, 2000; Marks *et al.*, 2001). It is also a useful adjunctive therapeutic agent in dogs receiving allergen-specific immunotherapy (Scott & Miller, 2007). PTX is rapidly absorbed and metabolized in dogs after oral administration, and well tolerated (Marsella, 2000). Fatty acids are increasingly used in canine atopy and other canine and feline dermatoses, and their beneficial effects are documented in several prospective, controlled studies (Bond & Lloyd, 1992a,b; Scarff & Lloyd, 1992; Logas & Kunkle, 1994; Mueller *et al.*, 2004). In some atopic dogs, fatty acids alone can alleviate the clinical signs, while in others, the use of fatty acids can reduce the amount of glucocorticoids required to control pruritus (Bond & Lloyd, 1994) or act synergistically with antihistamines (Paradis *et al.*, 1991; Paterson, 1995). The therapeutic effects of fatty acids occur either through reaction of true fatty acids themselves or through their activated derivatives called eicosanoid (Barrett & Bigby, 1995).

Because of low number of published studies, there is only fair evidence to support the recommendation of use of pentoxifylline for the treatment of canine atopic dermatitis. Clearly, this drug deserves additional studies for confirming its efficacy in managing canine atopic dermatitis. A number of clinical studies have been published evaluating fatty acid supplementation for the treatment of CAD. However, to the author's knowledge, none has used a combination of PTX and polyunsaturated fatty acids (PUFAs) in the therapeutic management of canine atopic dermatitis as an alternative treatment. The aim of this present study was to evaluate the efficacy of PDE inhibitor, pentoxifylline and its combination with PUFAs for therapeutic management of canine atopic dermatitis.

Thirty privately owned dogs (Nineteen intact males and eleven females) of 1- to 10-year-age groups were selected for study (12 Labrador retrievers, five Golden retrievers, three German shepherds, four Nondescripts, and two each of Boxers, Pomeranians and Pugs). All dogs were suffering with CAD for at least 6 months and diagnosed according to the diagnostic criteria proposed by Willemse (1986). These atopic dogs were randomly allocated to three groups (I, II and III). Group I ($n = 12$) was administered with pentoxifylline 20 mg/kg body weight, thrice a day, and group II ($n = 12$) with pentoxifylline 20 mg/kg body weight, thrice a day, + PUFAs (containing linoleic acid, linolenic acid and oleic acid each 50 mg, eicosapentaenoic acid 2.5 mg, docosahexaenoic acid 1.5 mg, and Gama Linoleic acid 0.5 mg)/kg body weight, twice a day. Placebo was administered to group III ($n = 6$). All treatments were administered in food for 60 days. The dogs were evaluated on days 0, 30, and 60. On all three occasions, dogs were evaluated clinically and their blood was collected for different estimations (for complete blood count, serum urea, creatinine, alanine aminotransferase, and aspartate aminotransferase). Three dogs were dropped out because of owner's noncompliance, one from group I and two from group III, and remaining 27 completed the study.

Complete anamnesis, and general physiological and complete dermatological examination were conducted. The initial diagnostic investigation included a standard biochemistry profile, a complete blood count, absence of skin infections or parasitic infestations, and absence of food hypersensitivity. All dogs were positive for intradermal test (IDT), none had been treated with antihistamines, antibiotics, antifungal, and/or topical therapies during the immediate preceding 15 days and with short acting steroids and PUFAs during 30 days. None was on immunotherapy. Two dogs, one from each of group I and II needed antibiotic therapies for 5 days, to manage secondary bacterial infection

and two animals from group I vomited after taking PTX and required antiemetic for 2 days. No other drug was administered during the study period. As the dogs were client-owned, it was impossible to standardize the diets for all animals. However, as per the owners, all the dogs were managed on similar diet (mainly boiled rice, milk and eggs, wheat chapatti, and cooked chicken meat).

The clinical evaluation of the dogs on days 0, 30 and 60, comprised of assessment of Canine atopic dermatitis extent and severity index (CADESI) as described by Willemse (1986) and Visual Analog Scale (VAS) for pruritus based on owner-derived data. In addition, side-effects were also addressed. Briefly, the CADESI involves the separate evaluation of erythema, lichenification, and excoriation, in a scale grading from 0 (absent) to 3 (severe) at 40 different body sites (score ranging from 0 to 360). The VAS was 10-cm-long vertical line, in which the top end represented absence of pruritus and the bottom end severe pruritus. The owners were asked to indicate on this vertical line where there dog's pruritus could be placed. The length (in mm) from top to the owner's sign was measured and used as a tool for quantifying the animal's pruritus (score ranging from 0 to 100).

Canine atopic dermatitis extent and severity index and VAS score for each group and each treatment day were pooled and the average was statistically analyzed. One-way Analysis of variance (ANOVA) was used to evaluate the difference between the two groups with time. A two-tailed P -value of 0.05 was considered significant. Pooled CADESI and VAS score for pruritus on days 0, 30 and 60 for group I, II and III is summarized in Table 1.

A 100% recovery of both CADESI and VAS score was observed in 3/11 dogs treated with PTX and 5/12 treated with PUFA + PTX on day 60. PTX + PUFA treated group revealed 56.75% and 47.76% reduction in CADESI and VAS pruritus scores on day 30, while the corresponding reduction on day 60 was 90.92% and 92.59% respectively. PTX-treated group revealed 38.78% and 43.34% reduction in CADESI and VAS pruritus scores on day 30, while on day 60, it was 84.81% and 90.40% respectively. The largest percentage reduction in CADESI and VAS scores from the base line occurred with PTX + PUFA treated group on day 60 as well as on day 30, was particularly evident in 5/12 animals. Reduction in CADESI and VAS scores for pruritus of group II and I revealed statistically significant ($P < 0.05$) difference on days 60 and 30, in comparison with scores pertaining on same days of group III. These scores were also significant ($P < 0.05$) for group II in comparison with scores pertaining for group I on day 60. However, there was no

Table 1. Clinical CADESI and VAS score for pruritus of group I, II, and III on day 0, 30, and 60

Groups	Age (mean, years)	CADESI day 0	CADESI day 30	CADESI day 60	VAS day 0	VAS day 30	VAS day 60
Group I	4.59	38.90 $\pm$ 4.24	23.81 $\pm$ 2.50*	4.27 $\pm$ 1.17*	58.72 $\pm$ 4.89	33.27 $\pm$ 3.31*	5.63 $\pm$ 1.50*
Group II	4.79	39.50 $\pm$ 3.20	17.08 $\pm$ 0.98*	3.58 $\pm$ 1.11*,†	59.66 $\pm$ 4.08	31.16 $\pm$ 4.56*	4.41 $\pm$ 1.43*,†
Group III	3.75	31.50 $\pm$ 2.39	31.50 $\pm$ 2.10	31.25 $\pm$ 2.49	56.75 $\pm$ 3.32	56.50 $\pm$ 3.92	54.75 $\pm$ 3.75

*Significant difference at $P < 0.05$ when values compared with group III value.

†Significant difference at $P < 0.05$ when values compared with day 60 values of group I.

statistically significant difference between group II and group I on day 30, but higher recovery was found in group II. PTX was found to be a useful nonsteroidal, antipruritic agent for many dogs with CAD (Scott & Miller, 2007). Our findings are in agreement with the same.

Concentrations of serum urea nitrogen and creatinine were found within the reference range in all groups on day 0 and no significant alteration was revealed during the study period. The serum enzyme activities in all groups for ALT and AST were slightly higher on day 0, reduction was revealed on day 30 and day 60, but changes were nonsignificant (data not shown) indicating that PTX may not have an untoward action on liver and kidney functions. Similar findings have been demonstrated by Rees and Boothe (2003). CBC values were also found within reference range on days 0, 30, and 60 (data not shown). During the study period, two animals from group 1 vomited after taking PTX, and no other adverse effects were observed. Our observations are in agreement with findings of Scott and Miller (2007).

Thus, it can be concluded that PTX can be used to manage CAD with very few adverse events like vomiting. Combination of PTX and PUFAs can be used as an alternative modality to manage CAD with higher recovery rate. It can also be recommended as an adjuvant therapy along with main therapeutics of CAD, such as cyclosporine and glucocorticoids. Further studies with large number of animals are needed to explore these findings and to examine the benefits of PTX and PUFAs as combined modalities in the treatment of CAD.

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